Organocatalytic Asymmetric Friedel-Crafts Alkylation to γ-Hydroxy α,β-Unsaturated Aldehyde

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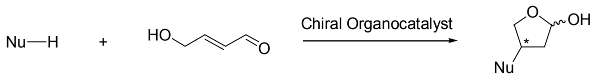
Enantiomerically pure γ-lactones are widely distributed in nature and many biologically active compounds.[1] In addition, chiral β-substituted γ-lactone chemistry plays a very important role in the synthesis of natural products.[2] Accordingly, numerous synthetic approaches to chiral β-substituted γ-lactones have been – and still are being – developed.[3] Chiral substituted tetrahydrofuran moiety has also been found in nature and many biologically active compounds including diazonimide[4] and the leptofuranin series.[5] However, to date, there have been reported very few methodologies for the synthesis of chiral substituted THF derivatives,[6] with even fewer synthetic methodologies of chiral 3-substituted THF heterocycles.[7] In this communication, we describe the facile synthetic strategy of chiral β-substituted γ-lactones and 3-substituted tetrahydrofurans by the reduction and oxidation of chiral β-substituted γ-lactols respectively, which are prepared by new catalytic asymmetric Friedel-Crafts alkylation of appropriate nucleophiles to a γ-hydroxy α,β-unsaturated aldehyde using an organocatalyst.[8,9]

Recently, we have reported the catalytic asymmetric 1,4-addition of arylvinyl- and arylboronic acids to γ-hydroxy α,β-unsaturated aldehyde using an organocatalyst to afford β-substituted γ-lactols.[10] Although arylvinylboronic acids were showed good yields with high enantioselectivities, arylboronic acids were appeared with low enantioselectivities. After being taken these results, we considered the protocol to obtain the high enantioselective β-aromatic substituted γ-lactols which was the Friedel-Crafts alkylation with appropriate nucleophiles to a γ-hydroxy α,β-unsaturated aldehyde instead of the 1,4-addition of arylboronic acids (Scheme 1).[11]

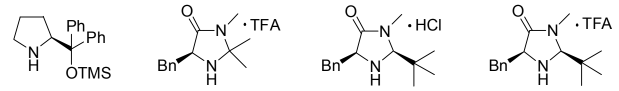
In this process, the Friedel-Crafts alkylation of *N*-methylindole (**4a**) to 4-hydroxy-but-2-enal (**2**) was selected as a model reaction. Diphenylprolinol silyl ether catalyst **I** (Figure 1) was initially examined in this reaction in CH_2Cl_2 at −10 °C (Table 1). However, the reaction was not proceeded to furnish the corresponding β-*N*-methylindole γ-lactol **5a** and the starting material was almost recovered after 18 hours (entry 1).

Next, we investigated other type of organocatalyst – imidazolidinone catalyst, which have been used to the many Friedel-Crafts alkylations of α,β-unsaturate aldehydes, in this reaction. First of all, imidazolidinone catalyst **II** was examined in the reaction of *N*-methylindole (**4a**) to 4-hydroxy-but-2-enal (**2**). The reaction was completed within 6 hours with 68 yield and moderate enantioselectivity (54% ee, entry 2). Moreover, second generation imidazolidinone catalyst **IV** show the increased reactivity and enantioselectivity (83% yield, 81% ee, entry 4), although the catalyst **III** provided the product in low yield (entry 3). After the reaction conditions were optimized (solvent system and temperature control), we found that the superior levels of enantioselectivity and yield were exhibited by catalyst **VI** in CH_2Cl_2 – *i*-PrOH at −40 °C (99% yield, 83% ee, entry 7).

Having established the optimal reaction conditions, we next probed the generality of this asymmetric catalytic reaction with various indoles to 4-hydroxy-but-2-enal (**2**) (Table 2). Variation in the *N*-substituent (R = Me, allyl, CH_2Ph, entries 1-3) is possible without significant loss in yield or enantioselectivity (≥ 95% yield, 82 ~ 87% ee). Incorporation of electron-donating substi-



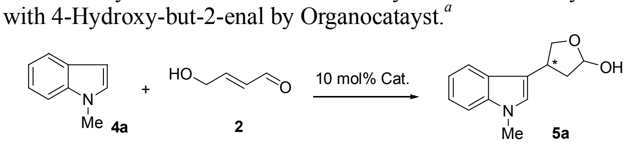
Scheme 1. Organocatalytic Friedel-Crafts alkylation with γ-Hydroxy α,β-Unsaturated Aldehyde.



I II III IV

Figure 1. Chiral Amine Organocatalysts.

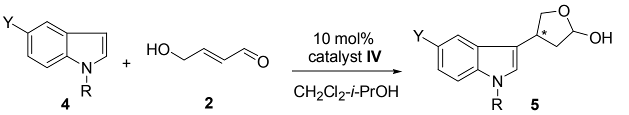
Table 1. Asymmetric Friedel-Crafts Alkylation of *N*-Methylindole with 4-Hydroxy-but-2-enal by Organocatayst.[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	I	CH_2Cl_2	−10	18	no rxn	-
2	II	CH_2Cl_2	−10	6	68	54
3	III	CH_2Cl_2	−10	6	10	-
4	IV	CH_2Cl_2	−10	3	83	81
5	IV	$CHCl_3$	−10	3	70	76
6	IV	CH_2Cl_2-*i*-PrOH (90:10 v/v)	−10	12	92	79
7	IV	CH_2Cl_2-*i*-PrOH (90:10 v/v)	−40	24	99	83

[a]Reactions were carried out in solvent (0.5 M) with 2.0 equiv of 4-hydroxy-but-2-enal relative to the *N*-methylindole in the presence of 10 mol% catalyst. [b]Isolated yield after chromatographic purification. [c]Determined by HPLC analysis after oxidation.

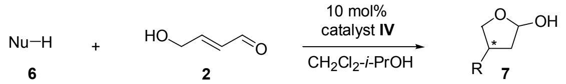
Table 2. Orgnocatalytic Friedel-Crafts Asymmetric Alkylation of Representative Indoles with 4-Hydroxy-but-2-enal.

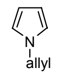
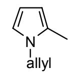
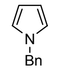
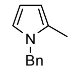
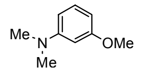
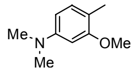
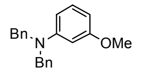
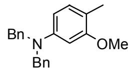
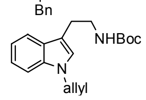
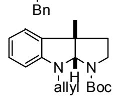
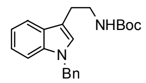
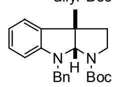
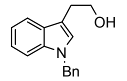
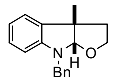


entry	indole substituents R	indole substituents Y	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	Me	H	−40	24	99	83
2	allyl	H	−40	24	95	82
3	CH_2Ph	H	−40	24	99	87
4	CH_2Ph	OMe	−30	24	97	82
5	CH_2Ph	OBn	−20	12	99	79
6	CH_2Ph	Br	−20	24	51	85

[a]Isolated yield after chromatographic purification. [b]Determined by HPLC analysis after oxidation.

Table 3. Orgnocatalytic Asymmetric 1,4-Addition of Representative Nucleophiles with 4-Hydroxy-but-2-enal.

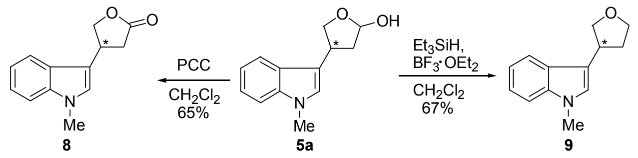


entry	Nu-H	R	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1			−40	2	44	70
2			−40	8	42	73
3[c]			−10	36	97	81
4[c]			−10	48	38	81
5[c]			−10	48	48	6
6[c]			−10	48	25	8
7[c]			−10	36	56	3

[a]Isolated yield after chromatographic purification. [b]Determined by HPLC analysis. [c]Carried out in CH_2Cl_2 and the presence of 20 mol% catalyst.

tuents (Y = OMe, OBn) at the C(5)-indole position slightly decreased reactivity and reaction selectivity, albeit with high yields (≥ 97% yield, 79 ~ 82% ee, entries 4-5). Electron-withdrawing substituted indole (Y = Br) was not proceeded to product completely, which still remained, after 24 hours at −20 °C (51% yield, 85% ee entry 6).

In order to broaden the scope for the reaction, we expanded our substrates to the nucleophiles possible to Friedel-Crafts alkylation (Table 3). Pyrrole derivatives (*N*-allyl, *N*-Bn) provided the corresponding γ-lactol with high reactivity and moderated enantiosectivity, even though isolate yields are low due to the decomposition of product (42 ~ 44% yield and 70 ~ 73% ee, entries 1 and 2). In the case of the reaction with electron-rich *N*,*N*-dialkyl anilines, the reactivity was diminished and then



Scheme 2. Elaboration of the β-substituted γ-lactol.

reaction was performed in CH_2Cl_2 at −10 °C. *N*,*N*-dimethyl 3-methoxyaniline gave the corresponding product in good yield (97%) and high enantioselctivity (81% ee, entry 3). When we used tryptamine and tryptophol as nucleophile in this reaction that expected to give pyrroloindoline and furanoindoline, unfortunately in all cases, poor levels of yield and enantioselection were observed (entries 5-7).

Finally, Scheme 2 outlines transformations of the β-substituted γ-lactol. β-substituted γ-lactone **8** and Chiral 3-substituted tetrahydrofuran **9** could be accessed in good yields by the oxidation and reduction of compound **5a** respectively.

In summary, we have communicated the catalytic asymmetric Friedel-Crafts alkylation of appropriate nucleophiles to a γ-hydroxy α,β-unsaturated aldehyde using an imidazolidinone as an organocatalyst which afforded β-substituted γ-lactols in good yields and with up to 87% ee.

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